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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/964,065	09/26/2001	Imre Kovesdi	212357	1431

23460 7590 02/27/2002

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EXAMINER
PRIEBE, SCOTT DAVID

ART UNIT	PAPER NUMBER
1632	5

DATE MAILED: 02/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/964,065	KOVESDI ET AL.	
	Examiner	Art Unit	
	Scott Priebe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 36-48 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 36-48 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The preliminary amendments filed 9/26/01 have been entered. Claims 1-35 have been cancelled. Claims 36-48 have been added. The preliminary amendment is not deemed to be part of the original disclosure, because the originally filed, signed declaration is a copy of the declaration filed in 08/258,416 and does not refer to the preliminary amendment. See MPEP 608.04(b) & 714.01(e).

Applicant should note that in addition to the 3 MONTH shortened statutory period for response to this action under 35 USC 133 to avoid abandonment of this application, a time limit of 3 MONTHS for response to this action is being concurrently set under 37 CFR 1.607(b) to avoid disclaimer of the instantly claimed invention. See MPEP 2307.02. While the shortened statutory period may be extended under 37 CFR 1.136(a), the time limit may not be extended.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in

the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

The instant specification, excluding the claims, is essentially identical to the specification filed with application 08/258,416. The instant claimed invention is not described or fully enabled either by the instant specification or the '416 specification for the reasons set forth below in the rejections under 35 USC 112, first para.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 36-43 and 45-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 36-43 and 45-47 each require a cell line whose genome comprises part of the adenoviral E4 region including ORF6, and lacking a "functional ORF4", which is broadly interpreted to mean that ORF4 is inactivated due to point mutation, deletion, insertion, etc. Claim 42 further limits claim 36 to an embodiment wherein ORF4 is not present at all, and claim 43 further requires that ORF1-ORF4 be absent from the cellular genome. While the specification as

originally filed supports the limitation regarding E4 sequences comprising ORF6, it does not support the limitation excluding a functional ORF4 or ORF1-ORF4 . There is no mention, even in passing, of a genus of cell line wherein ORF4 or ORF1-ORF4 are lacking or are non-functional. Thus there is no evidence of record that applicant had contemplated the instantly claimed embodiments at the time the 08/258,416 application was made. Furthermore, since the instant declaration does not refer to the preliminary amendment as being part of the specification, there is no evidence of record that the invention now being claimed was contemplated as being part of the invention of the instant application.

Claims 36-38, 40-43, and 45-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cell lines and methods wherein the adenovirus E4 region in the cellular genome is operably linked to an inducible or repressible promoter, does not reasonably provide enablement for embodiments wherein it is linked to a promoter which is not inducible or repressible. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 36-38, 40-43, and 45-47 recite no limitation on the promoter used to express adenoviral E4. The specification (paragraph bridging pages 14-15) describes the importance of using inducible or repressible promoters to express adenoviral sequences in the cell lines, specifically mentioning E2A and E4. All of the exemplified cell lines which are disclosed as

being capable of producing adenovirus lacking E2A or E4 have nucleic acid sequences encoding products complementing the E2A and E4 regions which are operably linked to an inducible promoter. The use of an inducible or repressible promoter which directs low levels of expression except when induced (or derepressed) is the only means taught in the specification for obtaining production of viable cells which can complement the E2A and E4 regions. The specification also teaches that repressible promoters can be used, rather than inducible promoters, where derepression is used to induce expression of E2A and E4 at the desired time.

Those skilled in the art recognized that expression of the E1, E2A and E4 genes is disruptive of normal cell metabolism, so that the transcription regulatory sequences used to control expression of the E2A and E4 genes in the host cells must be used which reduced expression to low levels during cell growth, and which can be induced to higher activity when the cells are used to produce the recombinant adenovirus (Klessig et al. (1984) Mol. Cell. Biol. 4(7), pp. 1354-55; Wang et al. (1995) Gene Ther. 2, pp. 779-780; and the Declaration of Dr. Kovesdi filed 5/13/96 in application 08/258,416, pp. 5-7). Armentano et al. (Hum. Gene Ther. 6: 1343-1353, 1995) in discussing the prior and post-filing art (page 1344, col. 1, full para. 1) disclose that despite extensive knowledge for development of adenoviral vectors, little success had been reported on vector genome modifications, being limited to deletions of E1 and E3. With respect to replication defective vectors, the reference discusses propagation of defective virus on complementation lines, and states that "This approach is problematic in principle due to the large number of structural and regulatory genes, many of which are temporally regulated, function

stoichiometrically, and may be toxic to cells at levels required for complementation." It also discloses that "the 293 cell line was difficult to produce initially and there are few, if any, reports of similar cell lines stably expressing E1 functions." Imler et al. (Gene Ther. 3(1): 75-84, 1996) disclose that "the exact nature of adenovirus sequences present in 293 cells is not known" (page 76, bottom of col. 1), and "many previous attempts to establish stable cell lines permanently expressing the E1 region failed, apparently owing to the toxicity of E1A gene products" (page 76, col. 2, full para. 1). Imler et al. disclose that while vectors expressing E1A under control of a constitutive promoter could be maintained in A549 cells, they could not be maintained in Vero cells (para. bridging pages 76-77).

Given the recognized cytotoxicity of the E1, E2A and E4 gene products, and given the lack of guidance in the specification regarding how to produce complementing cell lines using any type of promoter other than one which directs low levels of expression except when induced (or derepressed), undue experimentation would have been required by one skilled in the art at the time the application was filed to make or use the claimed invention except wherein the host cell nucleic acid sequences encoding products complementing the E4 region are operably linked to inducible or repressible promoters.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 36-43 and 45-47 are rejected under 35 U.S.C. 102(a) & (e) as being clearly anticipated by Vigne et al., US 6,127,175.

See claims 1, 3-5, 11, 12, 15, 16, 20, and 23-25, for example. This rejection is proper because neither the instant application nor the '416 parent application, as originally filed, provides a written description of the claimed embodiments, and as a result the instant application does not meet the requirements of 35 USC 120 for benefit of priority to the '416 application.

Claims 36-48 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kovesdi et al., US 5,851,806 or US 5,994,106.

See Examples 3 and 11 and Figures 2, 3 and 10 of the '806 patent and Examples 3, 4, 9 and 10 and Figures 2 and 3 of the '106 patent. This rejection is proper because neither the instant application nor the '416 parent application, as originally filed, provides a written description of

the claimed embodiments, and as a result the instant application does not meet the requirements of 35 USC 120 for benefit of priority to the '416 application. The intervening patents that claim priority to the '416 are now a statutory bar *vis a vis* the disclosed species embraced by the instant claims directed to a previously undescribed genus.

Claim 44 is rejected under 35 U.S.C. 102(b) as being anticipated by Weinberg et al. (Proc. Natl. Acad. Sci. USA 80: 5383-5386, 1983), as evidenced by Leza et al. (J. Virol. 63 (7): 3057-3064, 1989).

Weinberg et al. discloses pE4*gpt*16 which comprises the E4 region of Ad5, including ORF6 under control of the E4 promoter. The E4 promoter is an inducible promoter, see Leza et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 36-43 and 45-48 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9-17, 32-46 and 53-58 of U.S. Patent No. 5,851,806. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claim 48 embraces the claimed adenovirus of claims 9-17 and 53-58 of the '806 patent. When read in light of the specification, method claims 32-46 of the '806 patent embrace the same working examples embraced by instant claims 36-43 and 45-47, i.e. the cell line used has only ORF6.

Claims 36-43 and 45-48 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 7, 9-11, 14, 17, 19, 22 and 24 of U.S. Patent No. 5,994,106. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 36-43 and 45-48 embrace the subject matter of the claims of the '106 patent.

The following are provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Claims 36-48 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19, 20-26, 36-40, 43-56,

62-71, 76-95 of copending Application No. 08/258,416. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are directed to subject matter which embraces or is embraced by the claims of the '416 application.

Claims 36-43 and 45-48 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36-38, 52, 53, 68-70, 74, and 75 of copending Application No. 09/261,922. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '922 application embrace the subject matter of the instant claims, and the working examples also embraced by the instant claims.

Claims 36-43 and 45-48 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36 and 40-42 of copending Application No. 09/766,405. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '405 application embrace the subject matter of the instant claims, and the working examples also embraced by the instant claims.

Claims 36-43 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36-39 of copending

Application No. 09/797,064. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims either embrace the subject matter of the claims of the '064 application or *vice versa*.

Interference

Claims 36-43 and 45-47 of this application has been copied from U.S. Patent No. 6,127,175 for the purpose of an interference. Applicant has failed to specifically apply each limitation or element of each of the copied claim(s) to the disclosure of the application.

Furthermore, claims 36-47 of this application have been copied by the applicant from U. S. Patent No. 6,127,175. These claims are not patentable to the applicant for the reasons set forth above.

An interference cannot be initiated since a prerequisite for interference under 37 CFR 1.606 is that the claim be patentable to the applicant subject to a judgement in the interference.

Claim 48 of this application is asserted by applicant to correspond to claim 33 of U.S. Patent No. 6,127,175. Claim 48 is currently not patentable to Applicant, but would be allowable if the obviousness-type double-patenting rejections set forth above were overcome.

The examiner does not consider this claim to be directed to the same invention as that of U.S. Patent No. 6,127,175 because claim 33 of the '175 patent is directed to two individual species for each of Ad5, Ad2, Ad7 and Ad12, whereas instant claim 48 is drawn to a genus embracing these species as well as many other species. Applicant has provided no evidence or scientific reasoning as to why the issued claim would be obvious over the instant claim. In particular, there is no evidence of record that would provide motivation for one of ordinary skill in the art to delete the exact nucleotides from the specific adenoviral genomes recited in the issued claim, given the genus of the instant claim. See MPEP 2144.08 Accordingly, an interference cannot be initiated based upon this claim.

Conclusion

In addition to the shortened statutory period for response to this action set on the first page of this action, the PTO-326, under 37 CFR 1.607(b) applicant is given a time limit of THREE MONTHS from the mailing date of this communication to respond. Failure to respond within this time limit for response will, in the absence of a satisfactory showing, be deemed a disclaimer of the invention now being claimed. THE PROVISIONS OF 37 CFR 1.136 DO NOT APPLY TO THE TIME LIMIT SPECIFIED IN THIS ACTION.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX numbers are (703) 308-4242 or (703) 305-3014 for any type of communication. In addition, FAX numbers for a computer server system using RightFAX are

also available for communications before final rejection, (703) 872-9306, and for communications after final rejection, (703) 872-9307, which will generate a return receipt. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Deborah Clark, can be reached on (703) 305-4051.

Any inquiry concerning administrative, procedural or formal matters relating to this application should be directed to Patent Analyst Patsy Zimmerman whose telephone number is (703) 308-8338. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

John J. Doll, Director
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